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The Cytological Diagnosis of Gastric Cancer

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• **Established centers find that cytological study of gastric washings with saline or chymotrypsin, adequately performed, is a valuable diagnostic tool in the detection of early and curable gastric carcinoma.**

Our experience with a small series of 150 patients, studied by saline gastric washing, has emphasized the difficulties of collection and the particular importance of obtaining, by repeated washings if necessary, an adequate specimen of gastric epithelial cells for diagnosis, before an opinion is given.

It seems likely that the cytological method will be of future value in study of the natural history of gastric malignant disease and in detection of its surface lesions in their earliest form in asymptomatic, known-susceptible persons. Further, it should become a complementary part of the "stomach profile" in gastric diagnostic problems, where roentgenologic and gastroscopic studies may be expected to reveal the older, necrotic, or infiltrative lesions; cytological study, the earlier and more superficial stages of disease.

CANCER OF THE STOMACH, although declining in incidence, still accounts for approximately 7.8 per cent of cancer deaths in the United States, and the five-year survival rate after surgical operation for this condition, if patients with lymph node metastasis at the time of operation are included, is only 5 to 12 per cent. Without metastasis, subtotal gastric resection may produce five-year survival rates of 40 to 50 per cent.[6] The vital importance of new methods for early diagnosis is evident.[26]

It is fortunate that surface cells are readily desquamated from early carcinoma, either because there is less cement substance in malignant tissue, because growing cells beneath push them off or because there is necrosis which allows them to fall free.[17] Methods by which the presence of these cells is detected are capable of identifying extremely small and early lesions before they are grossly apparent to the surgeon or pathologist[11] and at a time when they would completely elude diagnosis by clinical means.

METHODS

The techniques and applications of exfoliative gastric cytology have been recently reviewed* and an excellent monograph on the subject has been written by Shade.[21] A review of reported methods[27] indicates that desquamated cells usually may be obtained by simple washing of the stomach with normal saline solution. All investigators have noted that a standardized, meticulous collection technique, performed by a dedicated person, is an important factor in success.

It is important to recognize that tumor cells are usually not exfoliated in a recognizable form from carcinomas which have become necrotic or ulcerated, even though these tumors may be so extensive that they are readily diagnosed by x-ray or gastroscopy.[4,16,18]

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*Reference Nos. 2, 5, 8, 9, 16, 19.

TABLE 1.—*Histologically Proven Benign Gastric Conditions (Findings by X-ray and Cytologic Study in 29 Patients)*

Number of Patients	Final Diagnosis	Diagnosis by X-ray: Diagnosis Uncertain	X-ray: Malignant (Proved Benign)	X-ray: Identified as Benign	Cytologic Study: Opinion Deferred†	Cytologic Study: False Positive	Cytologic Study: Identified as Benign
18	Benign ulcer	7	3	8	5	....	13
2	Gastric polyp	....	1	1	....	....	2
3	Chronic gastritis	2	....	1	1	....	2
3	Miscellaneous benign gastric conditions	2	....	1	1	....	2
3	No gastric disease	1	....	2	2	....	1
29	Total cases	12	4	13	9	0	20
	Per cent of cases	41	14	45	31	0	69

†Specimen inadequate to permit forming an opinion.

A skilled cytodiagnostician may examine one slide in 20 minutes, or six slides in two hours. The full time is required before a slide can be pronounced negative; a positive diagnosis can often be made after brief examination.

REPORTED RESULTS

Shade[20] reported that very superficial infiltration existed in 31 of 258 cases of carcinoma observed by him; and, of these, 18 were entirely unsuspected clinically and radiologically, and the diagnosis depended solely upon positive cytological findings.

False-negative results of cytological examinations are due to a failure to obtain or identify cancer cells in the smear and are frequently associated with the presence of gastric retention, submucosal tumor, or surface necrosis or ulceration of a tumor.[25] On the other hand, studies at established cytological centers have become so accurate that a negative report must be seriously weighed in the differential diagnosis of benign and malignant ulcers.[2,21]

Cytological false-positive is so infrequent that a positive report, particularly if repeated, is a valid indication for laparotomy.[22] The abnormal cell associated with healing gastric ulcer,[16] chronic gastritis, gastric atrophy, gastric polyposis, and the mucosal changes of pernicious anemia before cyanocobalamin treatment[14,17] have sometimes been misinterpreted. Malignant cells have been found in the gastric aspirate in cases of carcinoma of the gallbladder[7] or pancreas.[12]

Experienced observers are unanimous in recommending the cooperative use of all available methods in the diagnosis of gastric carcinoma. McHardy[15] expressed belief that earlier diagnosis may be achieved through an awareness of the importance of vague symptoms, achlorhydria remaining after administration of histamine, and the early use of cytological study. He cited a diagnostic accuracy of 95 per cent for competent cytodiagnosis, 95 per cent for radiological surveys in selected hospitals, 88 per cent for ambulatory x-ray screening, and 77 per cent for gastroscopy, performed with skill. It seems reasonable to assume that less than 5 per cent of early, operable gastric carcinoma should escape detection if all of the available methods, including cytology, are used skillfully and repeatedly.

USES OF GASTRIC CYTOLOGICAL STUDY

As the study of gastric cells is most applicable to detection of early and superficial gastric carcinoma, it was inevitable that it should be applied to screening processes.[15] In this respect special attention has been paid to certain groups found to have a higher than ordinary incidence of gastric cancer—for example, persons having Type A blood,[1,10] pernicious anemia,[9,11] a family history of gastric cancer,[5] or achlorhydria persisting after the administration of histamine.[3,12] The high incidence of gastric cancer among the Japanese qualifies them for special attention.

The method may also be used to identify postoperative recurrence of carcinoma in the stomach,[24] or to confirm the gastric origin of a neoplasm which is evident only by metastatic lesions.[13]

Ideally, cytological examination will take its place as an element in the construction of a "stomach profile" which will combine information from clinical, radiological, and gastroscopic sources with the analysis of acid production after histamine, and eventually with data on the uptake of radioactive phosphorus by the gastric mucosa[23] and the biochemical and metabolic concomitants of mucosal disease which are now coming under investigation.

PRELIMINARY REPORT ON PRESENT SERIES

Methods

An Ewald tube, lubricated with glycerin or water-soluble jelly, was introduced into the stomach after an overnight fast. No premedication was given unless gastroscopy was to be performed. Two hundred cc. of normal saline solution at room temperature was introduced with moderate force and the patient was immediately rolled prone and on each side, ending in the left lateral decubitus position with the

TABLE 2.—*Gastric Carcinoma (Findings in 11 Cases)*

Case	Age	Sex	Character of Lesion	Diagnostic Method					Cytologic Study	
				Histological Proof	Gastric Acid	Gastric Retention	X-ray	Gastroscopy	By WDJ	By AJL
1	90	F	Adenocarcinoma, antrum. No metastasis.	Yes	None	None	M	Not done	Def.	Pos.
2	56	F	At operation 2 months after cytologic study: Adenocarcinoma, lesser curvature with huge ulcer.	Yes	N	None	U Improved on medication Rx	Not done	Neg.	Neg.
3	43	M	Adenocarcinoma, fundus. Metastasis. Congenital gastric cysts.	Yes	L	None	B	B (polyposis)	Pos.	Neg.
4	81	F	Adenocarcinoma, antrum. Metastasis.	Yes	L	None	M	Not done	Pos.	Pos.
5	82	M	Adenocarcinoma, antrum. Metastasis.	Yes	H	Yes	M	Not done	Def.	Neg.
6	82	F	Adenocarcinoma, antrum. Metastasis.	Yes	L	Yes	M	Not done	Def.	Neg.
7	74	F	Adenocarcinoma, posterior wall. Metastasis.	Yes	L	Yes	U	Not done	Neg.	Neg.
8	49	F	At operation 1 month after cytologic study: Impression, primary carcinoma cardia with metastasis. Biopsy—liver fibrosis.	No Died 6 months	N	None	B	B Gastritis with ulcer	Neg.	Neg.
9	75	F	No operation. Carcinoma, fundus, with small ulceration.	No	None	None	M	Unsatisfactory (obstruction)	Pos.	Neg.
10	73	F	No operation. Carcinoma, fundus.	No Died 1 month	None	None	M	Not done	Pos.	Neg.
11	83	F	At operation 6 months after cytologic study: Anaplastic carcinoma (linitis plastica). Metastasis.	Yes	None	None	B	Uncertain (lymphosarcoma not completely excluded)	Neg. *	Neg.
Per cent of carcinoma diagnosed by x-ray, 55; per cent diagnosed by cytologic study, 45; per cent diagnosed by combined x-ray and cytologic study, 73.										

N=Normal.
L=Low.
H=High.

M=Malignant.
B=Benign.

U=Uncertain—Specimen adequate but pathologist unable to decide.
Def.=Deferred—Specimen inadequate to permit forming an opinion.

*Repeat cytology six months later, when malignant disease was obvious by gastroscopy and x-ray, was also negative.

head low. The wash material was drained from the stomach by gravity and manipulation of the tube, which was then withdrawn.

The lavage fluid was quickly poured into 50 cc. plastic centrifuge tubes and spun at 5,000 rpm. for 3 minutes in a Serval-type SP angle centrifuge brought to the patient's bedside. Cell buttons were smeared on 4 to 8 uncoated glass slides which were immediately immersed in ether and alcohol solution. Seven to ten minutes elapsed between the introduction of the saline solution into the stomach and fixation of the slide. In some cases, the sediment was suspended in Bouin's solution, and later embedded in paraffin block for examination.

Selection of Patients

Almost all the patients in this series had gastrointestinal symptoms. Four patients with proven pernicious anemia were referred for periodic screening studies. The lavages were done at a number of places between April 1958 and February 1961. One of us (WDJ) examined all slides and all of the cell blocks in the cases in which they were prepared. Slides prepared from patients at the San Mateo Community Hospital were divided at random into two sets, each of which was examined independently by a pathologist (WDJ or AJL).

Preliminary Results

One hundred and fifty-five gastric lavages were performed on 150 patients. The average duration of follow-up by February 1961 was six and a half months, with a range from 0 to 34 months. Gastroscopy was performed in 78 cases. All but three patients had upper gastrointestinal x-ray examination at approximately the time of cytological study; these examinations were performed by a number of radiologists and the radiological opinion recorded is that which was expressed at the time of the cytological study, even if after subsequent films the opinion was changed.

In the series of 44 cases in which two sets of slides were made from the same material, there were five cases of proven gastric carcinoma. Both pathologists identified one of these; in a second, one examiner found malignant cells in his material, while the other was unable to find such cells in his set of slides either at the first examination or upon review. No malignant cells were found by either observer in slides from three patients, two of whom had pronounced gastric retention, the other having a large area of ulceration superimposed upon the carcinoma.

In the series of 150 patients, 139 were considered to have either benign gastric lesions or none at all. Histological evidence of benignity was obtained in 29 cases (Table 1).

Eleven of the patients were classified as having gastric carcinoma (Table 2). Histological proof was present in eight, and laparotomy in another revealed what was thought to be extensive metastatic carcinoma originating in the stomach, although liver nodule biopsy showed only "fibrous tissue." This patient and two others were presumed to have gastric carcinoma with widespread metastasis, although histological proof was not obtained either before or after death.

Seventy-six patients underwent gastroscopy and roentgenologic and cytological studies. The diagnostic performance of these methods in the cases in which they were used is summarized in Table 3. In the 76 patients studied by all three methods, disagreement was noted between the initial diagnostic opinion and the ultimate diagnosis in 12 cases, which are outlined in Table 4.

Six of the patients had decided gastric retention at the time the specimens were taken. In these cases, only the specimen taken after constant Levine tube drainage was satisfactory, and three of the false-negative results were associated with gastric retention.

In 65 cases Bouin's paraffin block preparations were made of the cell button remaining after the smears had been made. Comparison of results of smear examination with results of examination of the material in the block emphasized that it is difficult to thoroughly sample cellular material and that smears might fail to show gastric epithelium which was present in the larger specimen.

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TABLE 3.—*Overall Diagnostic Performance of X-ray, Gastroscopy and Cytologic Study in 150 Cases*

Method	Number of Cases	Percentage			
		Correct	False Positive	False Negative	Uncertain
Cytologic Study..	150	90.7*	0	4.0	5.3*
X-ray	147	62.0	5.4	2.0	30.6
Gastroscopy	78	82.1	3.8	2.6	11.5†

*Opinion was originally deferred in eight cases.
†Examination unsatisfactory or diagnosis uncertain.

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TABLE 4.—*Gastric Lesions Studied by X-ray, Gastroscopy and Cytologic Study (Follow-up of 12 Cases)*

Case No.	Diagnosis			Diagnosis on Follow-up
	X-ray	Gastroscopy	Cytologic Study	
1	M	N	I	No apparent malignancy 8 months (clinical)
2	M	N	I	Normal stomach (surgical biopsy)
3	M	M	I	Benign ulcer (surgical resection)
4	M	M	I	Benign ulcer (surgical resection)
5	B	B	V	Gastric adenocarcinoma (surgical resection 1 week later)
6	U	U	I	Benign ulcer (surgical resection)
7	U	U	Deferred*	Benign ulcer (postmortem)
8	U	U	Deferred	Inflammatory infiltrate of stomach (surgical resection)
9	B	B	I	Apparent gastric carcinoma with metastases (surgical exploration 1 month later)
10	U	U	I	No apparent malignancy 13 months (clinical)
11	U	M	I	No apparent malignancy 10 months (clinical)
12	B	U	I	Anaplastic gastric carcinoma with metastases—linitis plastica (surgical biopsy 6 months later)

M=Malignant. B=Benign. N=Normal
U=Uncertain—Specimen adequate but pathologist unable to decide.
*Specimen inadequate to permit forming an opinion.

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